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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Issued Dated	**6,921,531**
Issued Date	**July 26, 2005**
Application Number	**10/025,936**
Filing Date	**December 21, 2001**
First Named Inventor	**BRIESEWITZ, ROGER**
Group Art Unit	**1651**
Examiner Name	**NAFF, DAVID M.**
Total Number of Pages in This Submission: **13**	Attorney Docket Number: **STAN-066DIV**

ENCLOSURES (check all that apply)

- ☐ Fee Transmittal Form
- ☒ **Credit Card Payment Form**
- ☐ Amendment / Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Documents
- ☐ Response to Missing Parts/ Incomplete Application
  - ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Assignment Papers *(for an Application)*
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☒ **Petition for Certificate of Correction (1 pg.)**
- ☒ **Certificate of Correction (1 pg.)**
- ☒ **Petition Under 37 C.F.R. §1.183 (1 pg.)**
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s
- ☐ After Allowance Communication to Group
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to Group *(Appeal Notice, Brief, Reply Brief)*
- ☒ **Copy of Notice of Recordation of Assignment recorded 08/15/2005 (6 pgs.)**
- ☐
- ☒ Other Enclosure(s) *(please identify below):*

Copy of First/Last Page of Issued Patent (2 pgs.)

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Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Signing Attorney/Agent (Reg. No.)	**EDWARD J. BABA, 52,581** **BOZICEVIC, FIELD & FRANCIS, LLP**
Signature	
Date	**October 14, 2005**

Certificate
OCT 21 2005
of Correction

EXPRESS MAIL LABEL NO. EV 687 633 597 US

OCT 24 2005

EXPRESS MAIL NO.: EV 687 633 597 US

PETITION UNDER 37 C.F.R. §1.183		
	Attorney Docket	STAN-066DIV
	First Named Inventor	BRIESEWITZ, ROGER
	Patent Number	6,921,531
	Issue Date	July 26, 2005
	Application Number	10/025,936
	Filing Date	December 21, 2001
Address to: Mail Stop DAC Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Title: *"ADMINISTERING BIFUNCTIONAL MOLECULES CONTAINING A DRUG MOIETY AND PRESENTER PROTEIN LIGAND FOR THERAPY"*	

Sir:

Applicants request that 37 C.F.R. 3.81(a) be waived to permit the correct name of the assignee to be provided. Applicants assert that the failure to include the correct assignee name on the PTOL-85B was inadvertent.

Upon granting of this petition, Applicants request that the accompanying petition for certificate of correction be forwarded to the Certificate of Corrections Branch.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. § 1.20, which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815 order number STAN-066DIV.

10/19/2005 HLE333 00000020 10025936
01 FC:1462 400.00 OP

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: October 14, 2005

By: _____
Edward J. Baba
Registration No. 52,581

BOZICEVIC, FIELD & FRANCIS LLP
1900 University Avenue, Suite 200
East Palo Alto, California 94303
Telephone: (650) 327-3400
Fax: (650) 327-3231

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PETITION FOR CERTIFICATE OF CORRECTION		
	Attorney Docket	STAN-066DIV
	First Named Inventor	BRIESEWITZ, ROGER
	Patent Number	6,921,531
	Issue Date	July 26, 2005
Address to: Mail Stop DAC Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Application Number	10/025,936
	Filing Date	December 21, 2001
	Title: *"ADMINISTERING BIFUNCTIONAL MOLECULES CONTAINING A DRUG MOIETY AND PRESENTER PROTEIN LIGAND FOR THERAPY"*	

Sir:

Transmitted herewith for filing is a Certificate of Correction for the above-identified patent to correct typographical errors contained within Claim 16 and the Assignee name. Please replace the Assignees' names from "The Board of Trustees of the Leland Stanford Jr. University, Palo Alto, CA (US); The Howard Hughes Medical Institute, Chevy Chase, MD (US)" with --**"The Board of Trustees of the Leland Stanford Jr. University, Palo Alto, CA (US)**--.

Enclosed is a copy of Assignment recorded on August 15, 2005 showing that Howard Hughes Medical Institute assigned all rights to The Board of Trustees of the Leland Stanford Jr. University. Also, enclosed is a copy of the front and last page of the issued patent showing the incorrect assignees and claim 16.

Applicants attach hereto the appropriate fee of $100.00 to cover the cost of this petition. The Commissioner is hereby authorized to charge any additional fees under 37 C.F.R. § 1.20, which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815 order number STAN-066DIV.

10/19/2005 HLE333 00000019 6921531
01 FC:1811 100.00 OP

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

By: _____
Edward J. Baba
Registration No. 52,581

BOZICEVIC, FIELD & FRANCIS LLP
1900 University Avenue, Suite 200
East Palo Alto, California 94303
Telephone: (650) 327-3400
Fax: (650) 327-3231

PTO/SB/44 (02-01)
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(Also form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO : 6,921,531
DATED : July 26, 2005
INVENTOR(S) : BRIESEWITZ, ROGER, et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the first page of the issued patent, the Assignees "The Board of Trustees of the Leland Stanford Jr. University, Palo Alto, CA (US); The Howard Hughes Medical Institute, Chevy Chase, MD (US)" should be replaced with the assignee **--The Board of Trustees of the Leland Stanford Jr. University, Palo Alto, CA (US)--**.

In Col. 38, Claim 16, line 30, please delete the word "the"; and
In Col. 38, Claim 16, line 31, please delete the word "the".

MAILING ADDRESS OF SENDER:

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RECORDATION DATE: 08/15/2005 REEL/FRAME: 016400/0823
NUMBER OF PAGES: 3

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).
DOCKET NUMBER: STAN-066DIV

ASSIGNOR:
HOWARD HUGHES MEDICAL INSTITUTE DOC DATE: 09/20/1999

ASSIGNEE:
THE BOARD OF TRUSTEES OF THE
LELAND STANFORD JUNIOR
UNIVERSITY
1705 EL CAMINO REAL
PALO ALTO, CALIFORNIA 94306-1106

SERIAL NUMBER: 10025936 FILING DATE: 12/21/2001
PATENT NUMBER: 6921531 ISSUE DATE: 07/26/2005
TITLE: ADMINISTERING BIFUNCTIONAL MOLECULES CONTAINING A DRUG MOIETY AND PRESENTER PROTEIN LIGAND FOR THERAPY

08/23/05 DOCKETED

OCT 24 2005

016400/0823 PAGE 2

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PATENT ASSIGNMENT

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08/15/2005
800020210

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	ASSIGNMENT OF ASSIGNOR'S INTEREST

CONVEYING PARTY DATA

Name	Execution Date
Howard Hughes Medical Institute	1999-09-20

RECEIVING PARTY DATA

Name	Street Address	Internal Address	City	State/Country	Postal Code
The Board of Trustees of the Leland Stanford Junior University	1705 El Camino Real		Palo Alto	CALIFORNIA	94306-1106

PROPERTY NUMBERS Total: 1

Property Type	Number
Application Number	10025936

CORRESPONDENCE DATA

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NAME OF PERSON SIGNING:	Edward J. Baba
DATE SIGNED:	2005-08-11

Total Attachments: 2
source=Assign1.tif
source=Assign2.tif

COPY

ASSIGNMENT	Attorney Docket Number	SUN-66P
	First Named Inventor: Roger Briesewitz	
	Title	Bifunctional Molecules..
	Filing Date	May 21, 1999
	Group Art Unit	1646
	Examiner	Unassigned

WHEREAS **the Howard Hughes Medical Institute**, a Delaware Corporation, ("Assignor") was assigned the rights to an invention and patent application filed thereon entitled **Bifunctional Molecules and Therapies Based Thereon**, for which an application for a United States Patent was filed on **May 21, 1999**, Application Serial no. **09/316,932**,; Stanford University docket number S97-144; and Howard Hughes Medical Institute reference number 022506-98-01295; and all continuation and division patent applications and Letters Patent that may issue thereon worldwide (the "Invention"); and

WHEREAS, Assignor has agreed to transfer to **The Board of Trustees of Leland Stanford Junior University**, a non-profit educational institution of the State of California ("Assignee") all of Assignor's interest in, to and under such patent application and all continuation and division applications and Letters Patent that may issue thereto (including foreign counterparts thereto); and

NOW THEREFORE, for good and valuable consideration, the receipt of which is hereby acknowledged, Assignor hereby sells, assigns and transfers to Assignee full and exclusive right, title and interest to the invention, Letters Patent that may issue thereon, and any continuation, division, extension, renewal, substitution, reissue, reexamined patent or foreign counterpart thereof for the full term or terms for which the same was granted.

Assignor hereby covenants that no assignment, sale or agreement transfer or encumbrance has been or will be made or entered into which would conflict with this assignment or sale.

Assignor further covenants that Assignee will, upon its request, be provided promptly with all pertinent facts and documents relating to said invention, said applications and said Letters Patent (including any continuation applications, divisional applications, foreign counterparts and patents issuing thereon), as may be known and accessible to Assignor and will testify regarding the same in any interference or litigation related thereto and will promptly execute and deliver to Assignee or its legal representative any and all papers, instruments or affidavits required to apply for, obtain, maintain, and enforce rights in, to and under said invention, said application, and said Letters Patent which may be necessary or desirable, without further compensation, but at the expense of Assignee, its successors, assigns or other legal representatives.

EXECUTED this 20th day of September 1999

ASSIGNOR
Howard Hughes Medical Institute

By: Gerald R. Crabtree
Gerald R. Crabtree
for myself and as an Agent of the Howard Hughes Medical Institution

S97-144C
HHMI 1295

APPOINTMENT OF INVESTIGATOR AS AGENT

COPY

Appointment by the Howard Hughes Medical Institute (the "Institute") of Dr. Gerald R. Crabtree, an investigator employed by the Institute, as its agent for the purpose of assigning certain rights to The Board of Trustees of the Leland Stanford Junior University (the "University").

WHEREAS, the Institute and the University collaborate in the active conduct of medical research pursuant to a Patent and Intellectual Property Agreement between them dated as of January 1, 1985 (the "Agreement");

WHEREAS, pursuant to the Agreement, the Institute has agreed to assign to the University the Institute's rights with respect to inventions, discoveries, improvements, and other intellectual property, whether patentable or copyrightable (each a "Subject Property"), conceived or reduced to practice in the course of the research program conducted under the Agreement by employees of the Institute;

WHEREAS, research conducted pursuant to the Agreement by Dr. Crabtree while employed by the Institute at the University has resulted in the invention of a certain Subject Property entitled "Enhancement of Drug-Target Affinities by Protein Based Enlargement of the Drug Surface," which may be the subject of a patent application (the "Invention"), and the Invention is a Subject Property; and

WHEREAS, the Institute wishes Dr. Crabtree to act as its agent for the purpose of assigning to the University the rights the Institute has in the Invention by reason of the research program conducted at the University,

NOW, THEREFORE, the Institute hereby appoints Dr. Crabtree as its agent for the purpose of assigning the rights the Institute has in the Invention by reason of the research program conducted at the University to the University in accordance with and subject to the conditions of the Agreement.

Executed July 14, 1998

HOWARD HUGHES MEDICAL INSTITUTE

By: _____
W. Maxwell Cowan, M.D., Ph.D.
Vice President and Chief Scientific Officer

ATTESTED:

_____
Joan S. Leonard, Esq.
Vice President and General Counsel and Secretary

S97-144
HHMI 022506-98-01295

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US006921531B2

(12) **United States Patent**
Briesewitz et al.

(10) **Patent No.: US 6,921,531 B2**
(45) **Date of Patent: Jul. 26, 2005**

(54) **ADMINISTERING BIFUNCTIONAL MOLECULES CONTAINING A DRUG MOIETY AND PRESENTER PROTEIN LIGAND FOR THERAPY**

(75) Inventors: **Roger Briesewitz**, Mountain View, CA (US); **Gerald R. Crabtree**, Woodside, CA (US); **Thomas Wandless**, Menlo Park, CA (US); **Gregory Thomas Ray**, Stanford, CA (US); **Kurt William Vogel**, Palo Alto, CA (US)

(73) Assignees: **The Board of Trustees of the Leland Stanford Junior University**, Palo Alto, CA (US); **Howard Hughes Medical Institute**, Chevy Chase, MD (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 88 days.

(21) Appl. No.: **10/025,936**

(22) Filed: **Dec. 21, 2001**

(65) **Prior Publication Data**

US 2002/0147133 A1 Oct. 10, 2002

Related U.S. Application Data

(62) Division of application No. 09/316,932, filed on May 21, 1999, now Pat. No. 6,372,712.
(60) Provisional application No. 60/086,451, filed on May 22, 1998.

(51) **Int. Cl.**[7] **A61K 38/52**; A61K 38/00; C12N 11/02; C07K 1/00; C07K 17/02

(52) **U.S. Cl.** **424/94.5**; 424/94.1; 514/2; 514/9; 435/177; 530/402; 530/812

(58) **Field of Search** 514/2, 9; 424/94.1, 424/94.5; 435/177; 530/402, 812

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(Continued)

Primary Examiner—David M. Naff
(74) *Attorney, Agent, or Firm*—Bret E. Field; Bozicevic, Field & Francis LLP

(57) **ABSTRACT**

Bifunctional molecules and methods for their use in the production of binary or tripartite complexes in a host are provided. The bifunctional molecule is a conjugate of a drug moiety and a presenter protein ligand. The molecular weight of the bifunctional molecule is less than about 5000 daltons. In the methods, an effective amount of the bifunctional molecule is administered to the host. In certain embodiments the bifunctional molecule binds to the presenter protein and a drug target to produce a tripartite complex, while in other embodiments the bifunctional molecule binds to either the presenter protein or the drug target, but not both, to produce a binary complex The subject methods and compositions find use in a variety of therapeutic applications.

23 Claims, 9 Drawing Sheets

cultures is inhibited in a concentration dependent fashion. When these cells are transformed with a vector that allows the inducible expression of human FKBP, the bacteria become less sensitive to the bifunctional molecule when FKBP is expressed. To demonstrate that this detoxification of the bifunctional molecule is based on binding to FKBP, increasing concentrations of FK506 are added to the culture medium. FK506 competes with the bifunctional molecule for FKBP binding so that increasing concentrations of free bifunctional moelcule are present which can inhibit DHFR. FK506 by itself has no effect on the growth of the bacterial cultures in the presence or absence of FKBP.

This assay demonstrates that the presence of FKBP protects cells from the DHFR inhibitory activity of pteridine-FKBP ligand bifunctional molecules. This observation is the basis for creating cell selective anti-microbials that show reduced toxicity in humans.

It is evident from the above results and discussion that the subject invention provides a powerful tool for improving the affinity and/or specificity and selectivity of drugs. As such, the subject method provides for the improvement of drugs currently in use, e.g. by reducing unwanted side effects. Furthermore, the subject methods can be used to improve drugs that have, until now, been clinically useless due to considerable toxicity in humans and animals. Therefore, the invention provides for the potential usefulness of the variety of previously discovered and discarded biologically active compounds. Accordingly, the invention provides an important advancement in pharmacological science.

All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. The citation of any publication is for its disclosure prior to the filing date and should not be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

What is claimed is:

1. In a method of administering a drug to a host in need of said drug, the improvement comprising:

administering to said host an effective amount of a bifunctional molecule of less than about 5000 daltons consisting of said drug or a fragment thereof linked to a ligand for a presenter protein endogenous to said host, wherein said drug binds to a drug target and said ligand binds to a presenter protein that is not said drug target.

2. The method according to claim **1**, wherein said host is a mammalian host.

3. The method according to claim **2**, wherein said mammalian host is human.

4. The method according to claim **1**, wherein said drug is a small molecule.

5. The method according to claim **1**, wherein said drug binds to an extracellular target.

6. The method according to claim **1**, wherein said drug binds to an intracellular target.

7. The method according to claim **6**, wherein said presenter protein ligand is a peptidyl prolyl isom rase.

8. The method according to claim **1**, wherein said drug moiety and ligand of said bifunctional molecule are joined by a linking group.

9. A method for producing a tripartite complex in a mammalian host, said method comprising:

administering to said mammalian host an effective amount of a bifunctional molecule of less than about 5000 daltons consisting of a drug moiety linked to a ligand for a presenter protein endogenous to said mammalian host, wherein said drug moiety binds to a drug target and said ligand binds to a presenter protein that is not said drug target to produce said tripartite complex of said drug target, bifunctional molecule and presenter protein in said mammalian host.

10. The method according to claim **9**, wherein said tripartite complex is produced intracellularly.

11. The method according to claim **9**, wherein said tripartite complex is produced extracellularly.

12. The method according to claim **9**, wherein said drug target is a protein.

13. The met hod according to claim **9**, wherein said endogenous presenter protein is selected from the group consisting of: peptidyl-prolyl isomerases, Hsp90, steroid hormone receptors, cytoskeletal proteins, albumin and vitamin receptors.

14. The method according to claim **9**, wherein said bifunctional molecule is administered as a pharmaceutical preparation.

15. The method according to claim **9**, wherein said drug moiety and ligand of said bifunctional molecule are joined by a linking group.

16. A method for producing an intracellular tripartite complex in a mammalian host, said method comprising:

administering to said mammalian host an effective amount of a bifunctional molecule of less than about 5000 daltons comprising a drug moiety linked to a endogenous presenter protein ligand, wherein the said drug moiety and the said endogenous presenter protein ligand bind to different intracellular proteins; to produce said intracellular tripartite complex.

17. The method according to claim **16**, wherein said endogenous presenter protein is selected from the group consisting of: peptidyl prolyl isomerases, Hsp90, steroid hormone receptors and cytoskeletal proteins.

18. The method according to claim **17**, wherein said endogenous presenter protein is a peptidyl prolyl isomerase.

19. The method according to claim **16**, wherein said drug moiety and ligand of said bifunctional molecule are joined by a linking group.

20. A method for enhancing the selectivity of a drug for an intracellular drug target in a first cell as compared to a second cell, containing the drug target said method comprising:

contacting said first and second cells with a bifunctional molecule of less than about 5000 daltons comprising said drug linked to a ligand for a presenter protein that is not said drug target present in said second cell but not in said first cell, wherein said drug binds to the drug target in said first cell and said ligand binds to the presenter protein in said second cell;

to produce a binary complex comprising said bifunctional molecule and presenter protein in said second cell wherein the drug does not bind to the drug target in the second cell, and to produce a binary complex comprising said bifunctional molecule and drug target in said first cell wherein the drug binds to the drug target in the first cell.

21. The method according to claim **20**, wherein said drug is an antimicrobial agent.

22. The method according to claim **20**, wherein said ligand is a peptidyl prolyl isomerase ligand.

23. The method according to claim **20**, wherein said drug moiety and ligand of said bifunctional molecule are joined by a linking group.

* * * * *